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EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT PAPER NUMBER

1624

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application N .

10/004,287

Applicant(s)

BROWNER ET AL.

Examiner

Venkataraman Balasubramanian

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 December 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-101 is/are pending in the application.
- 4a) Of the above claim(s) 3,5,45,47,68 and 96-101 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,6-41,43,44,46,48-67 and 69-95 is/are rejected.
- 7) ☒ Claim(s) 42 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_                      6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicant's election with traverse of Group II, claims 1-2,4,6-44,46,48-67 and 69-95 in Paper No. 7 is acknowledged.

Claims 3, 5, 45, 47, 68 and 96-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter.

Claims 1-2,4,6-44,46,48-67 and 69-95 will be examined to the extent they embrace the elected subject matter.

The traversal is on the ground(s) that it would not be serious search burden to search all the groups. This is not found persuasive because of reasons of record. As for traversal the following apply:

Applicants' argument that there is no serious search burden to examine all said groups is not entirely incorrect. First of all, applicants' invention as recited include bicyclic and tricyclic heterocyclic compound where core A embraces mono or bicyclic carbocyclic ring and heterocyclic ring generically with X, W as carbon or nitrogen independently. This generic definition includes therefore a large number of hetero and carbocyclic compounds. Thus the classification of these generic ring systems with above said substituents would be all over the classes and subclasses and it mandatory for the examiner to search all classes and subclasses. Contrary to applicants' urging it would not be possible with the limited fixed time available for the examiner to examine each case to thorough search. Searching all possible classes and subclasses embraced by the generic definition of A with X and W would of serious search burden.

Art Unit: 1624

The requirement is still deemed proper and is therefore made FINAL.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-67 and 69-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rheumatoid arthritis, does not reasonably provide enablement for any or all TNF- $\alpha$  mediated disorders including those yet to be discovered as due to TNF- $\alpha$ . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claims 64-67 and 69-95 are drawn to "treating an inflammatory, metabolic or malignant condition". The scope of the claims includes not only any or all conditions but also those condition yet to be discovered as due to IKK mediated TNF- $\alpha$  for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the inhibiting expression of TNF- $\alpha$  activity mediated by IKKK of the compounds provided in the specification pages 24 and 100-101. The instant compounds are disclosed to have inhibiting IKK mediated expression of TNF- $\alpha$  activity and it is recited that the instant compounds are therefore useful in treating any or all diseases where TNF- $\alpha$  activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests

Art Unit: 1624

are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as Alzheimer's disease, multiple sclerosis, psoriasis etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. The state of the art is indicative of the requirement for undue experimentation. See *Graninger et al. Curr. Opin. Rheumatol.* 13(3) 209-13, 2001 (PubMed Abstract provided) and *Shaw et al. Expert Opin. Investig. Drugs* 9(7) 1469-1478, 2000 (PubMed Abstract provided). In addition, applicants clearly admit that the IKK mediated inhibiting expression of TNF- $\alpha$  activity is still unclear. See page 2, lines 30-33

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors

Art Unit: 1624

include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require IKK mediated inhibiting expression of TNF- $\alpha$  activity.

2) The state of the prior art: A very recent publication expressed that treating disease by the inhibition of IKK mediated expression of TNF- $\alpha$  is still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of IKK mediated inhibiting expression of TNF- $\alpha$  activity are unpredictable and at best limited to modulation of rheumatoid arthritis.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to expression of TNF- $\alpha$  activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

Art Unit: 1624

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2,4,6-41,43-44,46,48-67 and 69-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. WO 98/47869.

Instant claims relate to a fused heterocyclic semicarbazones and thiosemicarbazones bearing a pyridine to which an additional hetero ring is attached. Wang et al. in formula I teaches several fused heterocyclic semicarbazones and thiosemicarbazones which generically include compounds embraced in the instant claims for treating CNS disorders.

See page 5 formula 1 and note the definitions of various variable groups, which overlap with instant fused heterocyclic ring bearing A and X and W. Particularly note X can be a direct bond and note A<sub>1</sub> and A<sub>2</sub> definition on page 6 include instant pyridine core. See pages 31-61 for examples 1-28 for compounds made.

Instant claims differ from the reference in requiring furan, thiophene and their benzofused analogs to be directly linked to an additional hetero ring. Wang et al. exemplify all such compounds.



However Wang et al. teaches the equivalency of exemplified heterocyclic semicarbazones and thiosemicarbazones bearing a heteroring linked through a X group with those wherein X is a direct bond in the definition of various variable group of X of formula I. See page 5, lines 19-20. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in heterocyclic semicarbazones and thiosemicarbazones as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

***Allowable Subject Matter***

Claim 42 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims would be allowed since specific species embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

***Conclusion***

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Art Unit: 1624

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

  
Venkataraman Balasubramanian

3/8/2003